REMARKS

Claims 14-15, 17, 20-21, and 28-41 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. The amendment to claim 32 corrected a typographical error and does not constitute new matter. Support for the Ab1 and xenogenic antibodies in the amended and new claims can be found throughout the specification a filed, for example, at paragraph 3 of page 2. Support for new claims 35-36 can be found throughout the specification as filed, for example, at pages 10-11, and therefore, do not constitute new matter. Support for new claim 38 can be found, for example, on page 12 of the specification as filed. Support for new claims 39-41 can be found, for example, on page 13 of the specification as filed.

Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

35 USC § 112, first paragraph

Applicants assert that claims 14-15, 17, and 20-21 cannot be rejected under 35 USC § 112, first paragraph under scope of enablement, and then further rejected for completely lacking enablement. Specifically, by issuing a scope of enablement rejection for claims 14-15, 17, and 20-21, the Examiner has acknowledged on the record that some subject matter of the claims as recited is enabled. Thus, Applicants assert that is incorrect to have a full enablement rejection for the same claims.

35 USC § 112, first paragraph, enablement

Claims 14-15, 17, 20-21, and 28-34 are rejected under 35 USC 112, first paragraph for allegedly lacking enablement.

Applicants have amended the claims to recite a binding agent that is an Ab1 (including a fragment thereof) solely to expedite prosecution of the remaining claims and reserve the right to prosecute any canceled subject matter in a continuing application. Applicants further assert that the cancellation is not an acquiescence to the Examiner's position, merely a desire to further prosecution of the remaining subject matter.

A. Rejection of Example 12

The Examiner has alleged that the invention as described and claimed in the above-identified application was not enabled. In particular, the Examiner alleges in the Office Action mailed February 27, 2002, that it is unpredictable that the claimed method could produce an immune response against prostate specific antigen in a host having prostate cancer, in view of Example 12. In this regard, the Examiner alleges that one could not deduce from the fact that the claimed AR47.47 induces anti-idiotypic antibodies against PSA in prostate cancer-free host that the claimed antibody AR47.47 would also induce anti-idiotypic antibodies in a prostate cancer host.

Further, the Examiner alleges that since PSA is a self-antigen, it is unpredictable that in human patients with prostate cancer, the claimed antibodies would produce adequate numbers of CTLs with high affinity, which are optimal for interacting with the antigen.

To clarify the record, Applicants assert that administration of AR47.47 (an Ab1 antibody) would induce production of anti-idiotypic antibodies that mimic PSA (Ab2 antibodies), which in turn, induce production of anti-anti-idiotypic antibodies against PSA (Ab3 and Ab3' antibodies) that have a therapeutic effect.

Applicants note for the record that the Examiner stated in Paper No. 12 that applicant is enabled for a method of treating prostate cancer comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 (of SEQ ID NO: 1) of PSA (when claims were drawn to circulating PSA).

As is supported by the Schultes Declaration (attached as Exhibit C), to the extent the subject application describes the method of making Ab3 and Ab3', the data of Example 12 would not be considered to teach away from the usefulness or to suggest the methods of pending claims were not fully enabled by the application. In particular, the animal model used in Example 12, as a model for prostate cancer in mice, differs from the expected progress of human prostate cancer. In mice, the disease progresses on a much more rapid timescale. Accordingly, the time frame of the experiment after initiation of treatment in that animal would be comparable to stages in the human disease that would generally be beyond effective treatment. Thus, it would be understood that the protocol of Example 12 is not designed to predictive of the likelihood of success or failure for treating human patients having prostate cancer. Rather, the animal model of Example 12 indicates that an immunotherapeutic approach may not be successful in very late stage disease when time to induce an immune response is insufficient or the patient's immune system is highly suppressed due to the presence of large tumor burden, and would be understood simply to be irrelevant, at worst, in that it does not reflect an appropriate model, and would not be taken to teach away from the claimed methods.

Based on well-known principles, it could be readily understood by practitioners in this field that Ab3 and Ab3' antibodies induced by the administration of the claimed AR47.47 (Ab1) antibody would be highly specific for PSA. These antibodies can be generated via the idiotypic network or via processing of an immune complex of AR47.47 and PSA. According to the idiotypic network, the binding region of AR47.47 is immunogenic and can induce antibodies that fit exactly in the binding site of AR47.47 and consequently are mirror images of the respective PSA epitope of AR47.47 (Ab2). These Ab2 are in turn immunogenic and can induce antibodies make contact with their binding site (Ab3). These Ab3 are generally equivalent to the Ab1 in that they bind to the same epitope as the Ab1. and, therefore, have the same specificity as the Ab1, e.g., specificity for PSA. Alternatively, AR47.47 can bind PSA in circulation and form an immune complex. Processing of these immune complexes can lead to production of PSA-specific antibodies that can bind to multiple epitopes on PSA or it can lead to activation of a cellular response to PSA. That PSA is a self-antigen is irrelevant with respect to the claimed methods because the application describes a method that breaks tolerance to self-antigens. It would have been expected at the time of filing that adequate numbers of CTLs with high affinity for PSA would be produced.

Based on the knowledge in the art at the time the present application was filed, one of ordinary skill in the art would readily appreciate that if the claimed antibody AR47.47 could induced anti-idiotypic antibodies against PSA, in a cancer free host, the claimed antibody would also be expected to induce anti-idiotypic antibodies against PSA in a host with prostate cancer. The presence of PSA, produced by the prostate cancer, is important for immune complex formation and induction of multiepitopic anti-PSA antibodies (Ab3') and T cells specific for

PSA. Therefore, it would be expected that anti-PSA antibodies could be more readily induced in a host with prostate cancer, or in a host with residual disease.

Applicants assert that the technology of anti-idiotypic antibodies (Ab3) was well known at the time of filing as is further evidenced by the state of the art.

(1) PB Chapman (*Semin Cancer Biol* 6(6): 367-374 (1995)) (Exhibit A) teaches that anti-idiotypic monoclonal antibodies can mimic both protein and non-protein antigenic epitopes. In animal models and patients, it is possible to induce immune responses against tumor antigens using anti-idiotypic mAb vaccines.

(2) Herlyn et al. (*Cancer Immunol Immunother* 43(2): 65-76 (1996)) (Exhibit B) teach that anti-idiotypic antibodies (Ab2) binding to the antigen-combining site of anti-tumor antibodies (Ab1) can induce anti-idiotypic antibodies (Ab3) that specifically bind to the tumor antigen recognized by Ab1. Ab2, mimicking tumor antigens, have been shown to induce anti-anti-idiotypic proliferative T lymphocytes of the helper and suppressor type, as well as cytotoxic lymphocytes.

A salient feature of the present invention that distinguishes it over the prior art is that the compositions produce a multi-epitopic Ab3 or Ab3' response to the tumor-associated antigen, PSA (see, for example, paragraph 1 of page 10 of the disclosure). Further, an unexpected and unobvious result of the experiments of the instant application is that the AR47.47 monoclonal antibody is effective when administered to a host in a low dose formulation (see new claims 38-41).

Given that the methodology relied on in the Examples and other teachings of the specification are commensurate in scope with the teachings of these and other references, the induction of Ab3 antibodies would have been considered both routine and predictable with a reasonable expectation of success at the time of filing as is evidenced by the references cited *supra* and further in view of the Schultes declaration.

B. Rejection of Example 11

The Examiner alleged that Example 11 is not an adequately predictive model of how the claimed method would perform in the treatment of human prostate cancer in that mice are treated with the claimed antibody prior to injection of a tumor cell line.

In view of the entire teachings of the subject application, Example 11 can be related to the expected results in human prostate cancer. Patients suffering from prostate cancer are routinely treated, enter remission, and occasionally have residual disease in which PSA levels would rise. To prevent a relapse, an immunotherapeutic approach using AR47.47 would be very useful. The experiments given in Example 11 very closely mimic such a stage of prostate cancer. The tumors in mice grow at a much faster rate than prostate cancer does in humans, and would progress to an incurable stage within a few weeks. However, it takes at least three vaccinations or 6-8 weeks to induce a protective immune response. Therefore, mice could not be immunized sufficiently if immunizations were started after the tumor was transplanted. The mice in Example 11 were administered the Ab1 antibody prior to tumor inoculation to present an adequate model of early human prostate cancer or human prostate cancer after primary treatment. No one skilled in the art would believe that complete remission in 100 percent of the animal models would be required in order to expect the subject treatment to be useful in human patients.

To the extent a patient experiences a recurrence of the disease, it would be expected that they could be re-treated with Ab1 antibodies to cause the patient to re-enter remission or see combination with alternative therapies. Ab3 induced by the renewed treatment would bind to newly formed tumor cells.

C. Rejection of Experiments 8, 13, and 10, 14

The Examiner alleged that it is not clear from experiments 8, 13, and 10, 14 that Ab3 are produced. Further, the Examiner has alleged that in experiments 8, 10, and 14, the negative controls have positive results for Ab3 and has argued the results make it unpredictable as to whether Ab3 is actually detected in the reported experiments.

Applicants assert that the "positive results" the Examiner points to in the negative controls of experiments 8, 10, and 14 are likely the result of an immunological reaction of the mice to injection of a xenogeneic tumor cell line. The PSA expressed by the tumor cell line is foreign to the mice, and consequently, mice produce antibodies to PSA as a result of tumor inoculation. Thus, it is not surprising or unexpected that some antibodies are present in the background of the negative controls. However, in successful experiments, the level of anti-PSA antibodies should be much higher than in controls, and that observation does not alter the overall teachings of the subject application. In experiments 8, 10, and 14, the Ab1 antibody (AR47.47) did not induce a protective immune response in the majority of animals, indicated by the fact that antibody titers are not higher in AR47.47 treated mice than in the controls. This is likely due to tumor implantation prior to the immunizations and insufficient time to immunize the mice appropriately. The finding underlines that it is important that AR47.47 treatment induces a

protective immune response. Without that, the treatment has no effect on tumor progression. That observation does not lead away from teachings of the subject application. No one skilled in the art would believe that complete remission in 100 percent of the animals models would be required in order to expect the subject treatment to be useful in human patients. More importantly, evaluation of different treatment schedules allows for selection of an appropriate cancer population. For AR47.47 treatment, the experimental data indicate that this treatment would be most useful in early stage disease or as an adjunct treatment after first-line therapy, but would unlikely to be successful in late stage disease.

D. Ab2 correlation with method for inducing an immune response.

The Examiner alleged that the presence of Ab2 does not correlate with the claimed methods for inducing an immune response to PSA in a patient, or for inducing a host to produce an Ab3 that specifically binds to PSA. The Examiner also alleged that the claims do not recite a method for inducing the production of Ab2 antibodies.

By the time the present application was filed, it was well-known and accepted in the art that administration of Ab1 antibodies induced the formation of Ab2 antibodies, which ultimately induced the formation of Ab3 antibodies in a patient. This is the so-called "anti-idiotypic network". The methods of the pending claims rely on this phenomenon but also represent an advancement over the art in the realization that the induction of an anti-idiotypic network generating anti-PSA antibodies includes not only Ab3, but also Ab3', which are induced by complexes of AR47.47 and tumor-antigens, such as PSA. The Ab3' response is a subset of an anti-PSA response wherein the anti-PSA antibodies recognize epitopes distinct from the Ab1 antibody on a multi-epitopic antigen such as PSA.

In view of the teachings of the subject application, it is expected that Ab3 and Ab3' antibodies would be successfully generated by the administration of Ab1 antibodies, and would bind to an epitope on circulating prostate specific antigen in a patient. The induction of Ab2 and Ab3 antibodies in other settings was routine in the art at the time of filing, and one of ordinary skill in the art would not have expected that any experimentation would be required to induce Ab2 and Ab3 antibodies by the claimed method. Further, induction of Ab2 and Ab3 by the claimed method has clearly been demonstrated throughout the application (see Examples 5, 6, 8, 10, and 11). As is disclosed in Example 10 of the application, a competitive binding assay demonstrated the presence of both Ab2 and Ab3 antibodies as also indicated by the competitive assays of Examples 7, 9, 11, and 12 (see, for example, page 32 of the instant application). Thus the experimental results observed indicate that Ab3 were successfully produced. Further, based on the state of the art at the time of filing and the disclosure of the specification as filed, one of ordinary skill in the art would reasonably expect production of Ab3 and Ab3' as a consequence of the anti-idiotypic network. The Examiner's allegation that the claims do not recite a method for inducing the production of Ab2 antibodies, and ultimately Ab3 and Ab3' antibodies, is therefore incorrect.

E. Antibody induction specific for tumor

The Examiner alleged that one would not have expected any significant amount of tumor-specific antibody (Ab3) would be produced in a host with a pre-existing tumor burden.

Applicants assert that by the time the present application was filed, it was well-known and accepted in the art that when Ab1 antibodies are administered to a patient, Ab3 antibodies are induced in sufficient amounts in the host with tumor burden to elicit an effective immune

response as is set forth in the Schultes declaration. Further, cancer patients produce PSA and the presence of antigen allows for immune complex formation between AR47.47 and PSA. Consequently, one skilled in the art would expect that a host with a pre-existing tumor burden would produce more anti-PSA antibodies than a host without tumor burden.

Finally, Example 8 and Figures 10A and 10B clearly show that mice immunized with AR47.47 produce anti-PSA antibodies that bind to full length PSA and SEQ ID NO: 1.

Applicants assert that the Examiner has not provided any factual evidence in the form of publications as to why the antibodies produced would not bind to SEQ ID NO: 1, or circulating prostate specific antigen comprising SEQ ID NO: 1. Therefore, Applicants assert the Examiner has not met the standards of the enablement rejection as set forth in MPEP 2164, and specifically MPEP 2164.03, 2164.04, and 2164.05. Applicants respectfully request that the Examiner either produces such evidence in the form of publications meeting the standards of a specific and credible nature, or an Examiner's affidavit.

Applicants respectfully request reconsideration and withdrawal of the rejection.

35 USC § 112, first paragraph, scope of enablement

Claims 14-15, 17, and 20-21 are rejected under 35 USC 112, first paragraph for allegedly failing to meet the scope of enablement requirement.

The Examiner stated on page 7 of the Office Action that one cannot predict that administration of a binding agent, e.g., a label, that binds to the epitope of antibody mAb 47.47 and produces an immune response to prostate specific antigen, because the structure of said

binding agent is totally unrelated to prostate specific antigen, and would not likely to produce anti-idiotypic and anti-anti-idiotypic antibodies based on the teachings of Stites et al.

Applicant respectfully assert that the specification at paragraph 2 of page 10 through paragraph 3 of page 11 provide numerous examples of binding agents that bind to the epitope of monoclonal antibody 47.47 and produce an immune response to prostate specific antigen.

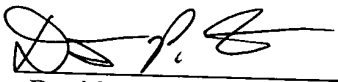
Nonetheless, Applicants have amended the claims to recite methods wherein an Ab1 is administered solely to expedite prosecution of the claims as amended, and reserve the right to prosecute any canceled subject matter in a future application.

Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



David Halstead
Reg. No. 44,735

Date: June 3, 2003

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050